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LETTER

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To the Editor:

We read the meta-analysis published by Knol and colleagues in Diabetologia with much interest [1]. The authors should be commended for their thorough work on this complex issue. However, one aspect of their work remains relatively poorly discussed, namely, the variety of methods used to measure depression and diabetes in their included studies. Although acknowledged as a study limitation, this issue has at least two important consequences we would like to discuss.

First, with regard to depression, the authors admit that the gold standard is a diagnostic interview schedule, but studies using weaker methods, such as self-report depression data, self-report 'semi-depression' data, and general practitioner's documented diagnosis of depression were also included in the meta-analysis. Except for one study [2], all used these relatively weak methods. Notably, the only study on the effects of formally diagnosed depression on diabetes incidence did not find a significantly raised risk (relative risk 2.23; 95% CI 0.90–5.55). The potential bias of not using a gold standard is easily illustrated: in a meta-analysis on the prevalence of depression in diabetes [3], a prevalence of depression of 11.4% was found when psychiatric interview data were used, compared with 31.0% when self-report scales were used ($p<0.0001$). Although the use of self-report instruments seems justified when looking at their sensitivity and specificity, their use is limited by the low positive predictive value of self-report measures (between 30 and 50%) (for example, see [4]), resulting in these overestimated prevalence rates. It remains to be determined to what extent these prevalence rates reflect treatable depression cases. Eventually, and as expressed by the authors, one would like to answer the question of whether preventing and/or treating depression prevents or delays the onset of type 2 diabetes. Since clinical guidelines and the intervention trials on depression (for example, see [5]) are based on a formal psychiatric diagnosis of depression, one may wonder whether the results of the study by Knol et al. can be used to address this issue.

Second, the authors tried to apply their findings to the aetiology of depression–diabetes comorbidity, and suggest several candidate mechanisms (e.g. increased activity of the hypothalamic–pituitary–adrenal axis, dysregulation of the immune system, and a low intake or impaired metabolism of omega-3 polyunsaturated fatty acids). However, in order to study these mediators in sufficient detail, diabetes should be scored on a continuous scale, e.g. using blood glucose levels, rather than using a binary standard. The presence of diabetes is nothing more than the crossing of a more-or-less arbitrary cut-off value for insulin resistance, which may be important for clinical purposes but is not very useful for aetiological questions. Not only does artificial dichotomising result in a loss of relevant inter-subject variation, but, as elegantly shown by Babyak [6], it can also result in spurious findings.

As such, the meta-analysis provides an overview of the existing literature on the possible link between depression and diabetes, but by doing so it shows that much remains unclear. Studies are urgently needed in which the methods used to determine depression and diabetes are adjusted to the question being addressed. The question, 'Can we prevent diabetes by treating depression?' can only be answered using diagnostic data on depression, and the aetiological question, 'Can depression cause diabetes?' can only be addressed using blood glucose levels.

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